

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. Serial No.: 10/666,366

Attorney Docket No.: 34506.143

Filing Date: September 19, 2003

Group Art Unit: 1652

Applicant(s): Huang et al.

Examiner: Richard G. Hutson

Title: **METHOD OF INACTIVATING RIBONUCLEASES AT HIGH TEMPERATURE**

Pre-Appeal Brief Request for Review

Mail Stop: AF

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

To the Commissioner:

Further to the Final Office Action dated July 3, 2008, and the Advisory Office Action dated September 26, 2008, Applicants request review of the Final Office Action and the Advisory Office Action prior to the filing of an appeal brief.

Applicants' Remarks begin on page 2 of this paper.

Applicants' Notice of Appeal is filed herewith.

Favorable reconsideration in view of the following remarks is respectfully requested.

REMARKS

Claims 1, 5, 7-10, 14-18, 22, 24-29, 31-35, 37-40, and 42-45 remain in the application. There is one rejection remaining in the case: All the pending claims currently stand rejected under §103(a) over Mizutani et al. (*Microbiol. Immunol.*, Vol 42(8), pp549-553, 1998) and Ambion, Inc., TechNotes 8(2) "SUPERase-In: The Right Choice for Protecting Your RNA," hereinafter "Ambion." Applicants traverse the rejection for the reasons now of record and respectfully request favorable reconsideration in view of these brief remarks.

Applicants respectfully traverse the rejection on two grounds. First, Applicants submit that the combination of references is improper, and, therefore, that the Office has not established a *prima facie* case of obviousness. Second, Applicants submit that the references in combination fail to teach or suggest all the required elements.

Claimed invention: The current claimed method involves heating an RNase inhibitor to temperatures as high as 90 °C to protect RNA from enzymatic degradation by RNases. Heating RNase inhibitors to such temperatures was unexpectedly found by the Applicants to increase its RNase inhibiting activity.

No benefit of combining methods taught in either reference: A first reason why combining the references is improper is because the references do not teach or suggest beneficial aspects of using an RNase inhibitor at high temperature. The Examiner references Mizutani et al. as teaching heating mixtures containing RNA to greater than 90 °C (see last paragraph on page 9 of Office Action dated December 10, 2007). Importantly, Mizutani et al. are silent with respect to RNases or any type of RNase inhibitor, a point acknowledged by the Office (see first full paragraph on page 7 of Office Action dated June 3, 2008). They are also silent with respect to any other means of mitigating effects of RNases in their RNA preparations. By contrast, the Examiner references Ambion as teaching adding RNase inhibitor protein to a solution containing RNA or to which RNA will subsequently be added (see first paragraph on page 10 of Office Action dated December 10, 2007). However, there is no technological reason or motivation to combine the two references to yield the invention as claimed. For example, Mizutani et al. teach an RT-PCR reaction, and at the point at which the solution is heated to greater than 90 °C, the stability of the RNA is immaterial to the outcome of the reaction, *i.e.*, amplification of the previously generated DNA. The Examiner has agreed with this point: "...at the point of the obvious [*i.e.*, Applicants'] method at which the temperature is raised to 90 °C, the RNase

inhibitor is no longer necessary” (see second full paragraph on page 7 of Office Action dated July 3, 2008). In addition, Ambion are silent regarding heating RNases above 67 °C. In fact, by explicitly stating an effective temperature range, Ambion provide an upper temperature bound with respect to efficacy of their RNase inhibitor and that of others: “SUPERase-In will effectively inhibit RNases from 4 °C to 65 °C, whereas RI loses activity at temperatures above 50 °C” (see section entitled “SUPERase-In Is Active Over a Broader Range of Conditions Than RI”). Ambion thus implicitly suggest that their RNase inhibitors, as well as other RNase inhibitors, will not work above 65 °C. There is absolutely no suggestion in either reference that adding an RNase inhibitor to a mixture containing RNA and heating it to temperatures above 65 °C will increase the RNase inhibitor’s activity. Therefore, any benefit of heating RNase inhibitors above 65 °C with respect to increasing inhibition activity is derived only from the present specification. Use of hindsight in combining references is improper. This traversal is covered on page 14, second paragraph, through top of page 15 of Applicants’ Response filed March 31, 2008.

References are silent with respect to—or teach away from—heating RNase inhibitors to currently claimed temperatures: A second reason why combining the references is improper is because the references are either silent to—or teach away from—heating RNase inhibitors to currently claimed temperatures. As mentioned, Mizutani et al. are silent with respect to RNases or any type of RNase inhibitor. Ambion teaches use of RNase inhibitors; however, Ambion not only teach 65 °C as an upper limit of RNase inhibitors’ effective range, they also teach against using RNase inhibitors at the claimed temperatures because such temperatures are taught to stimulate latent RNase activity in the inhibitors (see Figure 2 of Ambion and accompanying text).

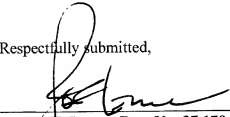
Applicants have submitted that this teaching away constitutes a ground against combining the methods described in the references. However, the Examiner has failed to explicitly address this issue on the merits. Instead, the Examiner provides the following circular argument: “...at the point of the obvious method at which the temperature is raised to 90 °C, the RNase inhibitor is no longer necessary” (see second full paragraph on page 7 of Office Action dated July 3, 2008). (The RNase inhibitor is no longer necessary because, as described above, the RNA would already have been reverse transcribed into DNA.) It is improper for the Examiner to assert a sought-after conclusion, *i.e.*, that the methods should be combined, as the premise in the

argument. Again, because “the RNase inhibitor is no longer necessary,” as is asserted by the Examiner, the benefit of heating RNase inhibitors around to 90 °C is taught only by the present specification. Use of hindsight in combining references is improper. This traversal is covered in the first and second full paragraphs on page 15 of Applicants’ Response filed March 31, 2008 and last paragraph on page 10 of Applicants’ response filed September 8, 2008.

References do not teach all required elements: Applicants submit that even if the references were to be combined, they fail to teach all the required elements of the claims. For example, Claim 1 not only requires adding an RNase inhibitor to a solution containing RNA or to which RNA will subsequently be added and heating the mixture to no less than about 90 °C; it also requires that the mixture **be heated for a time sufficient to inhibit RNase activity.** However, the combination of references fail to specify a time sufficient to inhibit RNase activity while heating the mixture to no less than about 90 °C. Ambion do not teach inhibition of RNase activity with RNase inhibitors at temperatures above 65 °C for any amount of time, and Mizutani et al. do not teach effects of RNase inhibitors at all. Thus, the combined reference fail to teach a **time sufficient to inhibit RNase activity**, and all the required elements are not met. Applicants therefore submit that the combination of references fails to render obvious Applicants’ claims. This traversal is covered on the first full paragraph on page 9 through the third full paragraph on page 10 of Applicants’ response filed September 8, 2008.

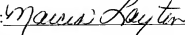
Conclusion: Applicants submit that this rejection is untenable. Withdrawal of the rejection is respectfully requested.


Respectfully submitted,


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PRE-APPEAL BRIEF REQUEST FOR REVIEW		Docket Number (Optional) 34506.143
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)] on <u>9 Oct 2008</u> Signature <u><i>Marcia Layton</i></u> Typed or printed name <u>Marcia Layton</u>		Application Number 10/666,366 Filed September 19, 2003 First Named Inventor Fen Huang Art Unit 1652 Examiner Hutson, Richard G.
Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request. This request is being filed with a notice of appeal. The review is requested for the reason(s) stated on the attached sheet(s). Note: No more than five (5) pages may be provided.		
I am the <input type="checkbox"/> applicant/inventor. <input type="checkbox"/> assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96) <input checked="" type="checkbox"/> attorney or agent of record. Registration number <u>37,170</u> <input type="checkbox"/> attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____		<div style="text-align: center;">  Signature Joseph T. Leone Typed or printed name (608) 255-8891 Telephone number <u>10/9/2008</u> Date </div>
NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*		
<input checked="" type="checkbox"/> *Total of <u>1</u> forms are submitted.		

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